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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHALEY, PABLO S	

ART UNIT	PAPER NUMBER
1631	

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07/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/016,616	GRUENBERG ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-16* is/are pending in the application.

4a) Of the above claim(s) *2,5 and 9-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, and 7-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' remarks, filed 04/23/2007, have been fully considered. The following rejections and/or objections are maintained, newly applied, or withdrawn for the reasons set forth below. They constitute the complete set presently being applied to the instant application.

STATUS OF THE CLAIMS

Claims 1, 3, 4, and 7-8 are herein under examination as they read upon the elected Species I-B (an optimization routine). Claim 6 has been cancelled. This application contains claims 2, 5, and 9-16 drawn to an invention nonelected with traverse in the response filed 01/09/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

PRIORITY

Priority to European Patent Office (EPO) Application No. 000123710.6, filed on 10/31/2000 has been acknowledged. The Examiner thanks the applicant for supplying a duplicate copy of the foreign priority document.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 7, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *These rejections are necessitated by amendment.*

Claims that depend directly or indirectly from claim 1 are also rejected herein due to said dependence.

Claim 1 (part c) has been amended to recite "wherein a ratio of the feed concentration...is calculated." Due to applicant's usage of passive language (e.g. "a ratio...is calculated"), it is unclear whether the above limitation is intended to be an active method step (i.e. calculating a ratio) or a further limitation of the claimed optimization routine. Clarification is requested via clearer claim language.

Claim 1 (part c) has been amended to recite "...the feed concentration of the complex nutrients and the total quantity of the complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously." Due to applicant's usage of passive language (e.g. "are treated", "are calculated and adjusted"), it is unclear whether the above limitation is intended to be active method steps (i.e. treating, calculating, adjusting), an intended use, or a further limitation of the claimed optimization routine. Furthermore, it is unclear in what way the said feed concentration and total quantity of complex nutrients are both related by a "ratio" and "treated as separate control variables that are calculated and adjusted simultaneously" in the same method step. Clarification is requested via clearer claim language.

CLAIM REJECTIONS - 35 USC §112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, 3, 4, and 7-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (a) calculating a feed concentration of the complex nutrients and (b) periodically stopping a supply of each nutrient, does not reasonably provide enablement for (c) adjusting the amount of each nutrient supplied to the microorganisms with an optimization routine, wherein a ratio of the feed concentration and the total quantity of the complex nutrients is calculated and the feed concentration of the complex nutrients and the total quantity of the complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. *This rejection is necessitated by amendment.*

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. While all of these factors are considered, a sufficient amount

for a prima facie case are discussed below which leads to the determination that the above claim lacks enablement due to undue experimentation being required to make and use the invention.

In the instant case, the claimed subject matter lacks enablement for the following reasons: Claim 1 is directed to a method of optimizing performance of a fermentation process involving a complex nutrient mixture. Claim 1 results in a step of adjusting the amount of each nutrient supplied to the microorganisms with an optimization routine, wherein a ratio of the feed concentration and the total quantity of the complex nutrients is calculated and the feed concentration of the complex nutrients and the total quantity of the complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously. Given the nature of the invention, one skilled in the art would require knowledge of the relationship between the claimed optimization routine and the claimed "ratio between the feed concentration of the complex nutrients and the total quantity of the complex nutrients." Furthermore, it is unclear how the amount of each nutrient supplied to microorganisms is optimized based on calculating the ratio of the feed concentration and a total quantity of the complex nutrients. No such guidance is set forth in the claims or disclosed in the specification. Therefore, it is unclear how the performance of a fermentation process is optimized by adjusting values with an optimization routine and the calculation of a ratio. [Wands factors (2), (4), (8)]. Methods for optimizing the performance of fermentation processes are known in the art. For example, Roubos et al. teach a method for optimization of fed-batch bioreactors using genetic algorithms [Abstract]. However, Roubos et al. do not provide guidance with regards to adjusting the amount of each nutrient supplied to the microorganisms with an optimization routine that is based on calculating a ratio of the feed concentration and the total quantity of the complex nutrients and treating the feed concentration and the total quantity of the complex nutrients as separate control variables.

Therefore, it would require undue experimentation by one of skill in the art to predictably practice the instantly claimed invention. [Wands factors (1), (2), (6), (7)].

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102 (b) as being anticipated by Roubos et al. (Journal of Biotechnology, January 1999, Vol. 67, p. 173–187). *This rejection is necessitated by amendment.*

Roubos et al. teach a method for optimization of fed-batch bioreactors using genetic algorithms [Abstract]. Roubos et al. specifically teach optimization results of a two-feed system wherein glucose, glutamine, and total feed concentrations are calculated over time [Fig. 6 and 7], and wherein glucose and glutamine are fed independently at a given ratio [p.180, Section 4.1], as in claims 1 (step a) and 2. Roubos et al. teach graphical representations that indicate periodic stoppage of feed rates of glucose and glutamine as controlled by optimization methods [Fig. 6], with specific preset minimization criteria (e.g. J values) [Fig. 7], as in claim 1 (step b). Roubos et al. also teach a double-feed reactor model for foreign protein production in bacteria (i.e. microorganism) using optimal control models [p.182, Section 4.2] comprising state variables comprising glucose, glutamine, and culture volume, control variables for volumetric feed rates of

glucose and glutamine, and kinetic expressions kinetic equations comprising feed and total volume concentration variables represented as $(F_1/V)*Glc_{in}$ and $(F_2/V)*Gln_{in}$ [p.185, Appendix B, Equations 2 and 3], which is a teaching for a ratio between feed concentrations and total quantity of complex nutrients, as in claim 1 (step c). Roubos et al. also teach dynamic iterative procedures (e.g. dynamic programming and GA) wherein changes in control variables are calculated and used to dynamically adjust the control trajectories iteratively [p.174, Col. 2, ¶ 3] and [Fig. 6 and 7], as required by claim 1 (step c).

Claims 1, 3, 4, 7, and 8 were rejected under 35 U.S.C. 102 (b) as being anticipated by Fleury et al. (Advances in Bioprocess Engineering, 1994, p.313-320).

Applicant's arguments, filed 04/23/2007, that Fluery et al. do not teach the limitation wherein "a ratio of the feed concentration and the total quantity of the complex nutrients is calculated and the feed concentration of the complex nutrients and the total quantity of the complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously" are persuasive. This rejection is hereby withdrawn.

Claims 1 and 3 were rejected under 35 U.S.C. 102 (a) as being anticipated by Miskiewicz et al. (Biotechnology Letters, 22: 1685-1691, 2000).

Applicant's arguments, filed 04/23/2007, that Miskiewicz et al. do not teach the limitation wherein "a ratio of the feed concentration and the total quantity of the complex nutrients is calculated and the feed concentration of the complex nutrients and the total quantity of the

complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously" are persuasive. This rejection is hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, and 7-8 are rejected under 35 U.S.C. 103(a) as being obvious by Kurokawa et al. (Biotechnology And Bioengineering, Vol. 44, No. 1, 1994), in view of Fleury et al. (Advances in Bioprocess Engineering, 1994, p.313-320).

Applicant's arguments, filed 04/23/2007, that Kurokawa et al. do not teach the limitation wherein "a ratio of the feed concentration and the total quantity of the complex nutrients is calculated and the feed concentration of the complex nutrients and the total quantity of the complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously" are not persuasive for the following reasons.

As set forth in the previous office action, mailed 10/26/2006, Kurokawa et al. teach a method for simultaneously controlling glucose and glutamine concentrations using an adaptive-control algorithm (i.e. optimization routine) comprising the following:

- Equations for calculating feed concentrations of complex nutrients [p.95, EQNs 1-3] and an adaptive control algorithm (i.e. optimization routine) for adjusting the feed rates from real-time data at every sampling time [p.98, col. 2, lines 29-32], as in amended claim 1(a) and the elected species.
- Simultaneous supply of at least two complex nutrient mixtures [p.96, col. 2, lines 1-3], as in instant claims 1(a) and 3.
- Positive, negative, and zero slope feed rates [Fig. 3], which correlates to alternately and periodically starting and stopping nutrient supply and on-line measuring and adjusting feed rates to decrease inhibitory metabolite activity by a certain concentration [p.99, col. 1, paragraph 2], which correlates to instant claim 1(b).
- Equations comprising independent model parameters and ratios of feed concentrations and working volumes (i.e. total quantity) of nutrients [p.97, Col. 2, ¶ 3, and p.98, Col. 1, ¶ 1 and 2] and [p.97 and 98, EQNs (9)-(12)], as in amended claim 1(c), which equates to a teaching for a ratio calculated as in claim 1 (step c).
- Generation of time-variant flow charts and response times based on three control algorithms comprising control variables [Fig. 2 and 3], as in instant claim 4(a) and (b).
- Input variables comprising distinct response times represented as quotients [p.97, Equation (7)], as in instant claim 4(c).
- Separate and simultaneous adjust of nutrient feed rates and concentrations [Fig. 3(b) and (c)] and [Table II], which correlates to instant claim 6.

Kurokawa et al. do not specifically teach the limitations of claim 7 and 8. However, Kurokawa et al. but do suggest the use of such control models with fermentation processes involving microorganisms [p.95, col. 2, paragraph 3].

Fleury et al. teach a multi-feed system and modeling and control strategies for the transformation of D-sorbitol to L-Sorbose using the microorganism *Gluconobacter oxydans* (i.e. *suboxydans*) [p.313, col. 1, paragraph 1], as in claims 7 and 8.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the invention of Kurokawa et al. using the microorganism *Gluconobacter oxydans* as taught by Fleury et al., as the production of antibody fragments in microbial cells is well known in the art [Kurokawa et al., Introduction]. One of ordinary skill in the art would have been motivated to combine the above teachings in order to increase productivity in fermentation processes using microorganisms, as taught by Fleury et al. [p.95, ¶ 3], resulting in the practice of the instant claimed invention with a reasonable expectation of success. One of ordinary skill in the art would have had a reasonably expectation of successfully combining the above teachings as Fleury et al. have already developed an online glucose and ethanol analyzer system in fed-batch cultures of microorganisms [p.95, ¶ 3]. This rejection is therefore maintained.

Claims 1, 3, 4, 7, and 8 are rejected under 35 U.S.C. 103(a) as being obvious by Fleury et al. (Advances in Bioprocess Engineering, 1994, p.313-320), in view of Major et al. (Biotechnology and Bioengineering, 1989, Vol. 34, p.592-599).

Applicant's arguments directed to Fleury et al. have been considered but are moot in view of the new grounds of rejection.

Fleury et al. teach an optimization strategy for the fermentation process directed to the microbial bioxidation of D-sorbitol to L-Sorbose (Abstract). More specifically, Fleury et al. teach the following aspects of the instantly claimed invention:

- Calculating multiple feed concentrations (s_1, s_2, H_20) supplied to a microorganism [Fig. 2], as in instant claim 1(a).
- Implementation of a delay before starting control actions to allow a minimal convergence of the state observer to values near the "real" state vector [p.318, col. 2, lines 28-34 and Fig. 4], which correlates to "periodically and alternately stopping a supply of each nutrient...until a metabolic activity of the microorganism decreases by a preset percentage" as in instant claim 1(b).
- Adjusting nutrient delivery using a non-linear model to design a control strategy [p.317, col.1, lines 21-32], which correlates to an optimization routine as in instant claim 1(c).
- Use of sorbitol and yeast extract (s_1, s_2) [p.314], which correlates to a complex nutrient mixture with different nutrients as in instant claim 3.
- Optimization routine generating a flow chart using negative-pulse response [p.319, col. 2, Fig. 5], as in instant claim 4(a).
- Time-variant flow charts of controlled and non-controlled systems with demonstrating negative-pulse response (Fig. 4 and Fig. 5), as in instant claim 4(a), (b).
- Control actions involving feed pumps using time values [Fig. 1], as in instant claim 4(c).
- Use of the microorganism *Gluconobacter oxydans* (i.e. *suboxydans*) [p.313, col. 1, paragraph 1], as in instant claim 7.
- Microbial oxidation of D-sorbitol to L-sorbose [p.313, col. 1, paragraph 1], as in instant claim 8.

Fluery et al. do not specifically teach "a ratio of the feed concentration and the total quantity of the complex nutrients is calculated and the feed concentration of the complex nutrients and the total quantity of the complex nutrients are treated as separate control variables that are calculated and adjusted simultaneously" as in claim 1. However, Fluery et al. do teach determining the biomass concentration (i.e. x) [p.314, Col. 1, Mass Balance Equations Section].

Major et al. teach a method of cell recycle fermentation (CRF) applied to lactate production in a microorganism [Abstract]. More specifically, Major et al. teach steady-state equations for calculating biomass concentration [p.595, EQN 2] based on feed concentration and recycle ratios (R) p.595, Table IV] and a molar product ratio [p.596, Table V], as in claim 1. Major et al. also teach peristaltic pumps for supplying growth medium (i.e. glucose) and controlling parameters for fermentation were set by manipulation of the speed of growth and filtrate pumps [p.594, Col. 1, ¶ 2].

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the feed concentration optimization process taught by Fluery et al. with the recycle ratio method taught by Major et al., where the motivation would have been to fine tune fermentation process parameters to obtain desired process optimization [Major et al., p.592, Col. 2, ¶ 1], resulting in the practice of the instant claimed invention with a reasonable expectation of success. One of ordinary skill in the art would have had a reasonably expectation of successfully combining the above teachings as both teach methods for optimization the fermentation process.

CONCLUSION

No claims are allowed.

Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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7/23/07